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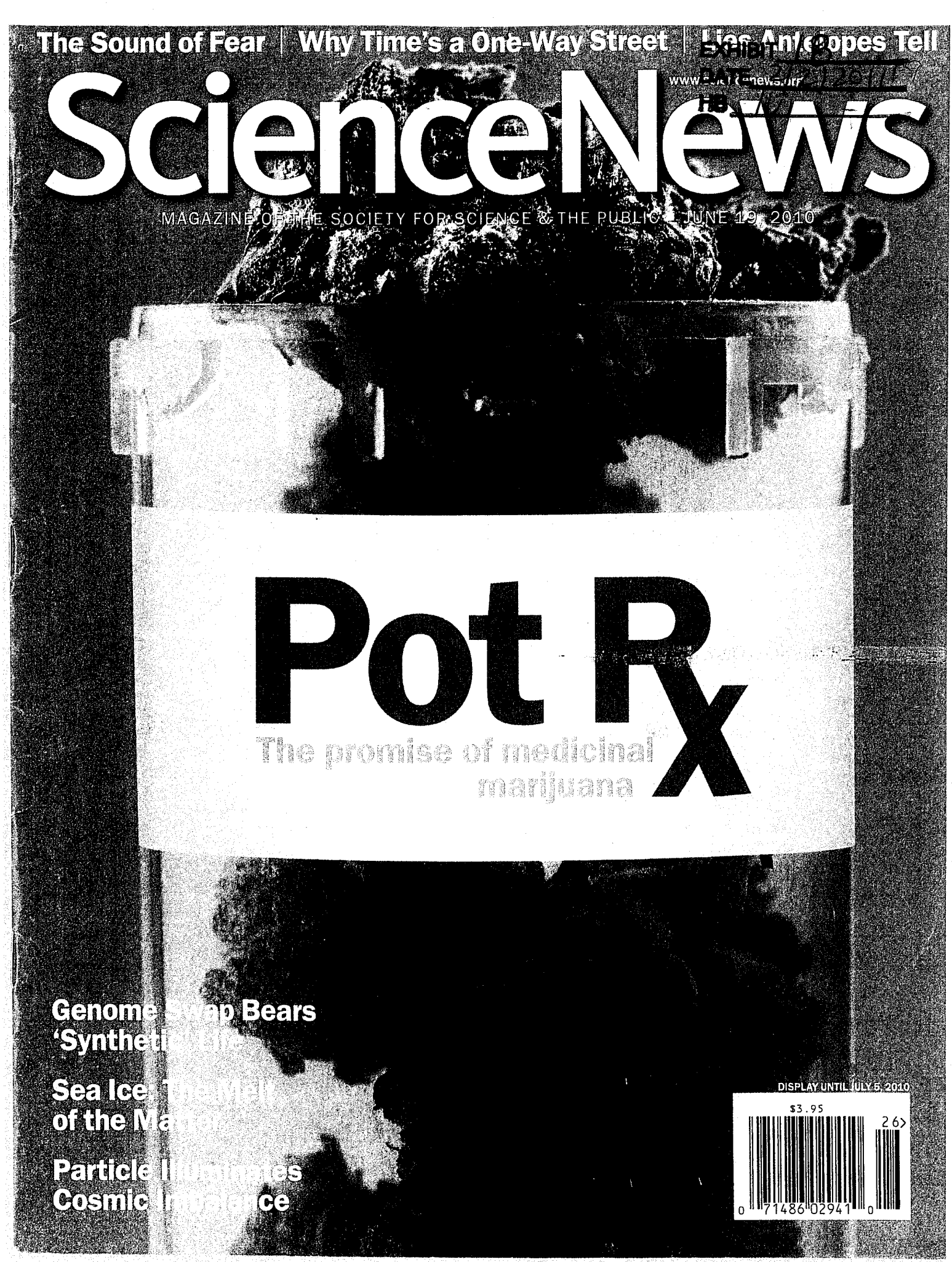
ScienceNews

MAGAZINE OF THE SOCIETY FOR SCIENCE & THE PUBLIC | JUNE 19, 2010



Pot Rx

The promise of medicinal marijuana

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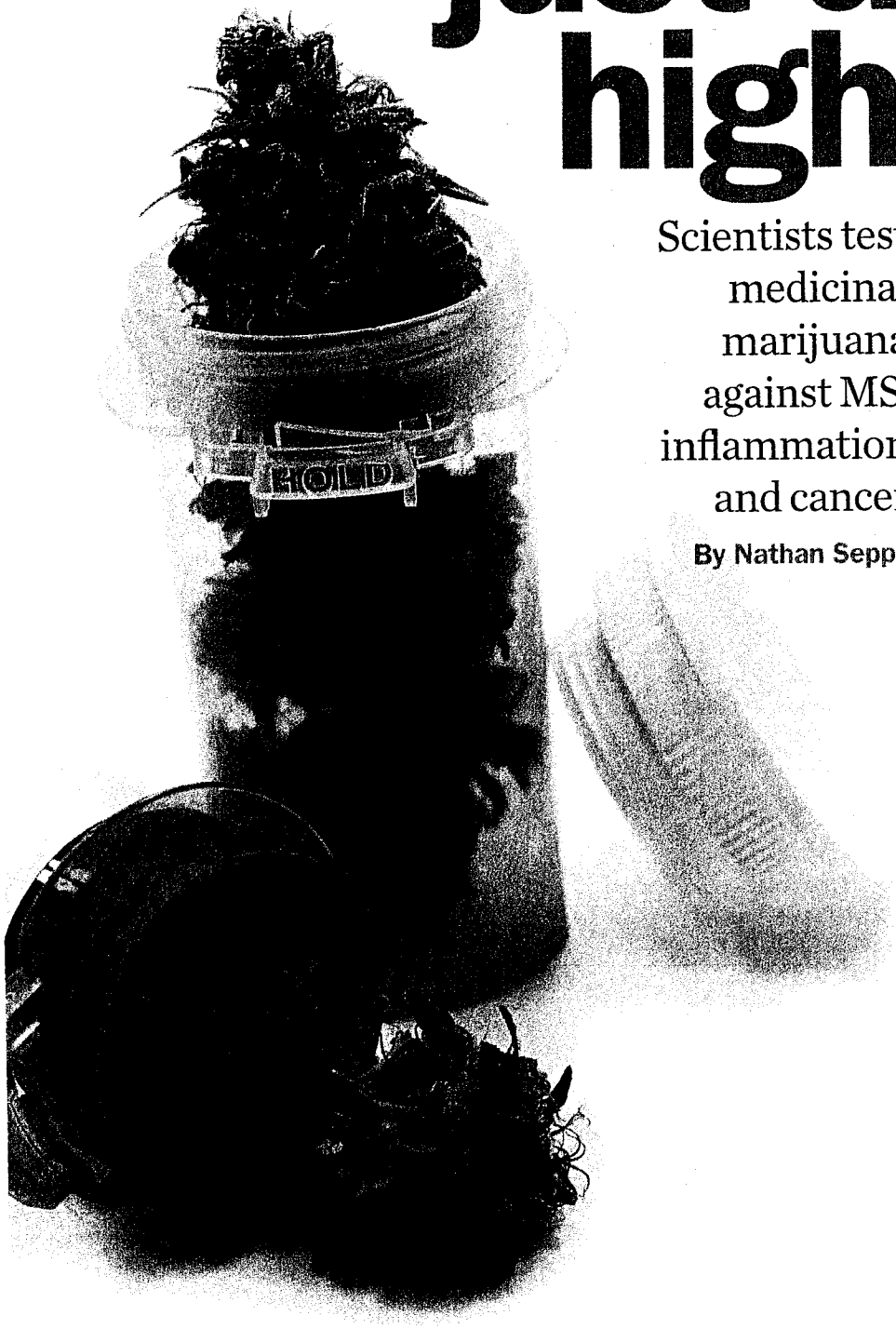
Not just a high

Scientists test medicinal marijuana against MS, inflammation and cancer

By Nathan Seppa



KATSGRAPHICSLV/ISTOCKPHOTO

In science's struggle to keep up with life on the streets, smoking cannabis for medical purposes stands as Exhibit A.

Medical use of cannabis has taken on momentum of its own, surging ahead of scientists' ability to measure the drug's benefits. The pace has been a little too quick for some, who see medicinal joints as a punch line, a ruse to free up access to a recreational drug.

But while the medical marijuana movement has been generating political news, some researchers have been quietly moving in new directions — testing cannabis and its derivatives against a host of diseases. The scientific literature now brims with potential uses for cannabis that extend beyond its well-known abilities to fend off nausea and block pain in people with cancer and AIDS. Cannabis derivatives may combat multiple sclerosis, Crohn's disease and other inflammatory conditions, the new research finds. Cannabis may even kill cancerous tumors.

Many in the scientific community are now keen to see if this potential will be fulfilled, but they haven't always been. Pharmacologist Roger Pertwee of the University of Aberdeen in Scotland recalls attending scientific conferences 30 years ago, eager to present his latest findings on the therapeutic effects of cannabis. It was a hard sell.

"Our talks would be scheduled at the end of the day, and our posters would be stuck in the corner somewhere," he says. "That's all changed."

Underlying biology

The long march to credibility for cannabis research has been built on molecular biology. Smoking or otherwise consuming marijuana — Latin name *Cannabis sativa* — has a medical history that dates back thousands of years. But the euphoria-inducing component of cannabis, delta-9-tetrahydrocannabinol, or THC, wasn't isolated until 1964, by biochemist Raphael Mechoulam, then of the Weizmann Institute of Science in Rehovot, Israel, and his colleagues. Within two decades, other researchers had developed synthetic THC to use in pill form.

The secrets of how THC worked in the body lay hidden until the late 1980s, when researchers working with rats found that the compound binds to a protein that pops up on the surface of nerve cells. Further tests showed that THC also hooks up with another protein found elsewhere in the body. These receptor proteins were dubbed CB_1 and CB_2.

A bigger revelation came in 1992: Mammals make their own compound that binds to, and switches on, the CB_1 receptor. Scientists named the compound anandamide. Researchers soon found its counterpart that binds mainly to the CB_2 receptor, calling that one 2AG, for 2-arachidonyl glycerol. The body routinely makes these compounds, called endocannabinoids, and sends them into action as needed.

"At that point, this became a very, very respectable field," says Mechoulam, now at Hebrew University of Jerusalem, who along with Pertwee and others reported the anandamide discovery in *Science*. "THC just mimics the effects of these compounds in our bodies," Mechoulam says. Although the receptors are abundant, anandamide and 2AG are short-acting compounds, so their effects are fleeting.

In contrast, when a person consumes cannabis, a flood of THC molecules bind to thousands of CB_1 and CB_2 receptors, with longer-lasting effects. The binding triggers so many internal changes that, decades after the receptors' discovery, scientists are still sorting out the effects. From a biological standpoint, smoking pot to get high is like starting up a semitruck just to listen to the radio. There's a lot more going on.

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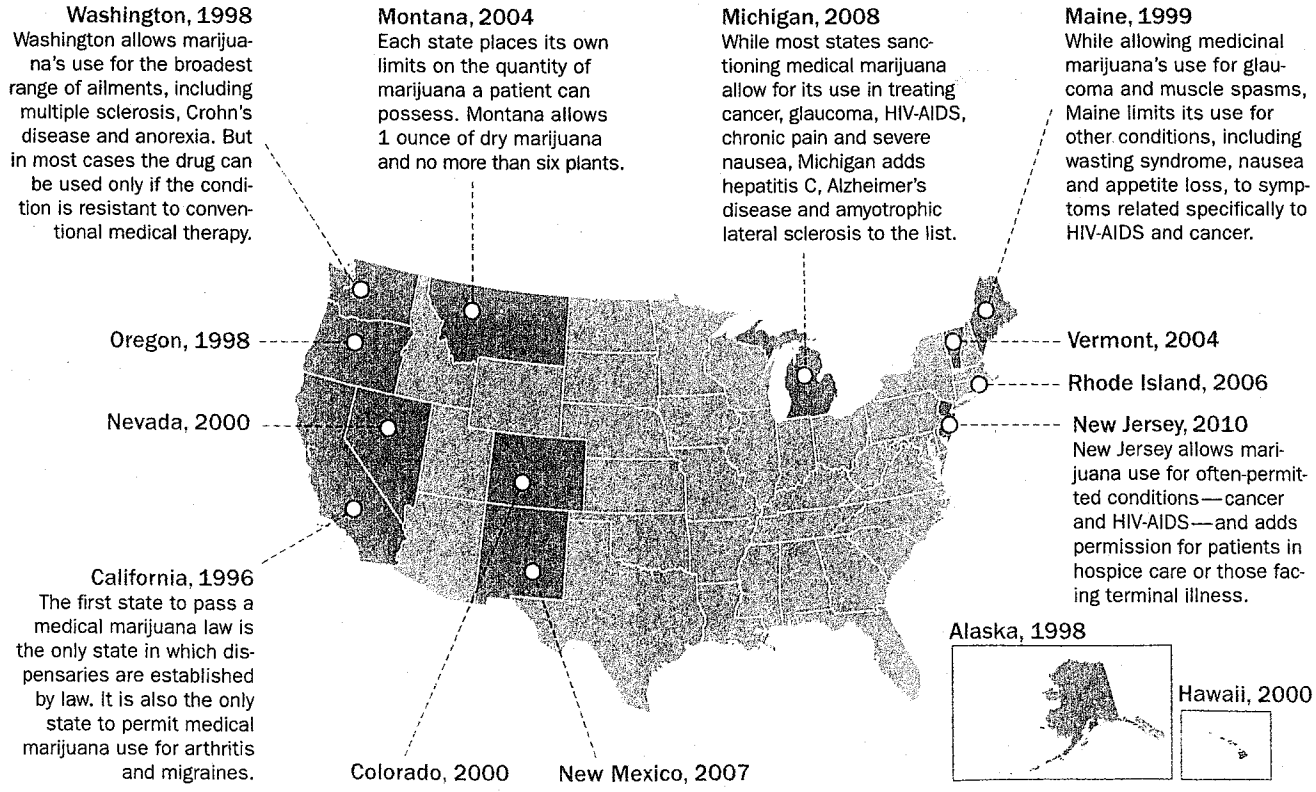
Though the psychoactive effect of THC has slowed approval for cannabis-based drugs, the high might also have brought on a serendipitous discovery, says neurologist Ethan Russo, senior medical adviser for GW Pharmaceuticals, which is based in Porton Down, England. "How much longer would it have taken us to figure out the endocannabinoid system if cannabis didn't happen to have these unusual effects on human physiology?"

Beyond the pain

Today smoked cannabis is a sanctioned self-treatment for verifiable medical conditions in 14 U.S. states, Canada, the Netherlands and Israel, among other places. It usually requires a doctor's recommendation and some paperwork.

People smoke the drug to alleviate pain, sleep easier and deal with nausea, lack of appetite and mood disorders such as anxiety, stress and depression. Patients not wanting to smoke cannabis can seek out prescriptions for FDA-approved capsules containing cannabis

Sanctioned smoking Though smoked cannabis has not been approved by the Food and Drug Administration, its use for medical purposes has been sanctioned by law in 14 states (shown in green, year given). Different states apply their own restrictions, some of which are highlighted.



KELLY ANN McCANN; SOURCE: D.E. HOFFMANN AND E. WEBER/*NEJM* 2010

compounds for treatment of some of these same problems.

Research now suggests that multiple sclerosis could join the growing list of cannabis-treated ailments. More than a dozen medical trials in the past decade have shown that treatments containing THC (and some that combine THC with another derivative called cannabidiol, or CBD) not only ease pain in MS patients but also alleviate other problems associated with the disease. MS results from damage to the fatty sheaths that insulate nerves in the brain and spinal cord.

"MS patients get burning pain in the legs and muscle stiffness and spasms that keep them awake at night," says John Zajicek, a neurologist at the Peninsula College of Medicine and Dentistry in Plymouth, England. Patients can take potent steroids and other anti-inflammatory drugs, but the effects of these medications can be inconsistent.

Pertwee has analyzed 17 trials in which MS patients received some form of cannabis or its derivatives. Reports from the patients themselves, who didn't know if they were getting real cannabinoids or a placebo in most of the trials, show improvements in muscle spasticity, sleep quality, shakiness, sense of well-being and mobility. Pertwee, who is also a consultant for GW Pharmaceuticals – which makes a cannabinoid drug that is delivered in spray form, called Sativex – reviewed the findings in *Molecular Neurobiology* in 2007.

Sativex was approved in Canada for MS in 2005 after studies (some included in Pertwee's analysis) showed its success in relieving symptoms of the disease. GW Pharmaceuticals expects clearance for MS treatment in the United Kingdom and Spain this year. Later, the company plans to seek U.S. approval of Sativex for cancer pain.

Zajicek's team has also compared MS patients who received a placebo with patients receiving either a capsule containing THC or one with THC and CBD. Both of the cannabis-based drugs outperformed a placebo, and the researchers are now working on a multiyear MS trial.

Calming symptoms such as muscle spasticity and pain is useful, Zajicek says, but the true value of cannabinoids may exceed that. "To me, the really exciting stuff is whether these drugs have a much more fundamental role in changing the course of MS over the longer term," he says. "We've got nothing that actually slows progression of the disease."

Fighting inflammation

CBD, the same cannabis component that proved beneficial alongside THC for MS, may also work on other hard-to-treat diseases. Tests on cell cultures and lab animals have revealed that CBD fights inflammation and mitigates the psychoactive effects of THC.

Crohn's disease, which can lead to chronic pain, diarrhea and ulcerations, could be a fitting target for CBD. In Crohn's disease, inflammatory proteins damage the intestinal lining, causing leaks that allow bacteria in the gut to spread where they shouldn't. This spread leads to a vicious cycle that can trigger more inflammation.

Karen Wright, a pharmacologist at Lancaster University in England, and her colleagues have found that CBD inhibits this inflammation and can reverse the microscopic intestinal leakiness in lab tests of human cells. Adding THC doesn't seem to boost the benefit, Wright reported in December 2009 in London at a meeting of the British Pharmacological Society. The results bolster earlier findings by Wright's team showing that cannabinoids could improve wound healing in intestinal cells.

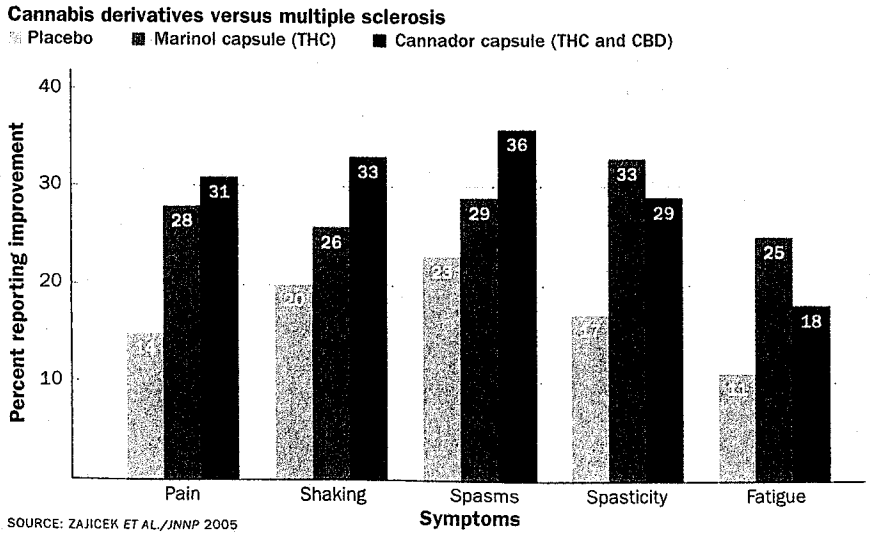
CBD's anti-inflammatory effect may work, at least in some cases, through its antioxidant properties – the ability to soak up highly reactive molecules called free radicals, which cause cell damage.

In the brain and eye, CBD slows the action of microglia, immune cells that can foster harmful inflammation when hyperactivated by free radicals. Working with rats whose retinas were induced to have inflammation, biochemist Gregory Liou of the Medical College of Georgia in Augusta and his team found that CBD neutralized free radicals, preventing eye damage. This finding could have implications for people with diabetes who develop vision loss.

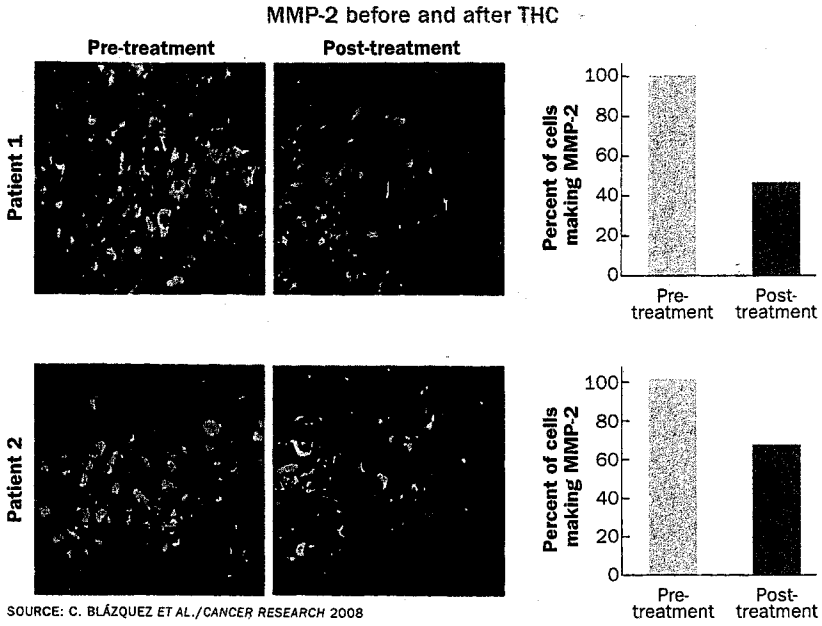
Apart from being an anti-inflammatory and antioxidant, CBD tones down the psychoactive effect of THC without eliminating its medical properties. CBD also mutes the occasional anxiety and even paranoia that THC can induce. This has been welcome news to scientists, who consider the "buzz" of cannabis little more than psychoactive baggage.

But CBD has paid a price for this anti-upper effect. "CBD has essentially been

Expanding its reach Scientists are investigating cannabinoids' potential against previously unconsidered medical problems—including inflammation, Crohn's disease and MS (shown below).



SOURCE: ZAJICEK *ET AL./JNNP* 2005



SOURCE: C. BLÁZQUEZ *ET AL./CANCER RESEARCH* 2008

Cancers with documented sensitivity to cannabinoids

Tumor type	Effect
Lung carcinoma	Decreased tumor size, less cell proliferation
Glioma	Decreased tumor size, programmed cell death
Thyroid epithelioma	Decreased tumor size, less cell proliferation
Lymphoma/leukemia	Decreased tumor size, programmed cell death
Skin carcinoma	Decreased tumor size, programmed cell death
Uterus carcinoma	Less cell proliferation
Breast carcinoma	Less cell proliferation
Prostate carcinoma	Programmed cell death
Neuroblastoma	Programmed cell death

SOURCE: GUZMÁN/*NATURE REVIEWS* 2003

Tumor suppression In patients with aggressive brain tumors, THC seems to knock down MMP-2 (green in images above left), an enzyme that facilitates cancer's spread by breaking down tissues. Cannabinoids also affect other cancer cells in rodents and in lab-dish experiments (see table).

bred out of North American black market drug strains," Russo says. People growing cannabis for its recreational qualities have preferred plants high in THC, so people lighting up for medical purposes, whether to boost appetite in AIDS patients or alleviate cancer pain, may be missing a valuable cannabis component.

Cannabis versus cancer

With or without CBD, cannabis may someday do more for cancer patients than relieve pain and nausea. New research suggests THC may be lethal to tumors themselves.

Biochemists Guillermo Velasco and Manuel Guzmán of Complutense University in Madrid have spent more than a decade establishing in lab-dish and animal tests that THC can kill cancer of the brain, skin and pancreas.

THC ignites programmed suicide in some cancerous cells, the researchers reported in 2009 in the *Journal of Clinical Investigation*. The team's previous work showed that THC sabotages the process by which a tumor hastily forms a netting of blood vessels to nourish itself, and also keeps cancer cells from moving around.

THC achieves this wizardry by binding to protein receptors on a cancerous cell's surface. Once attached, the THC induces the cell to make a fatty substance called ceramide, which prompts the cell to start devouring itself. "We see programmed cell death," Velasco says. What's more, noncancerous cells don't make ceramide when they come into contact with THC. The healthy cells don't die.

Many compounds kill cancer in a test tube and even in animals, but most prove useless because they cause side effects or just don't work in people. The Madrid team is now seeking funding to test whether cannabis derivatives can kill tumors in cancer patients. In an early trial of nine brain cancer patients whose disease had worsened despite standard therapy, the scientists found that THC injections into tumors were safe to give.

Early reports from other research groups suggest that THC also fights breast cancer and leukemia. "I think the cancer research is extremely promising," Russo says. "Heretofore, the model for cancer was to use an agent that's extremely toxic to kill the cancer before it kills you. With cannabinoids, we have an opportunity to use agents that are selectively toxic to cancer cells."

Looking ahead

Testing of cannabis and its derivatives has also begun on type 1 diabetes, rheumatoid arthritis, stroke, Tourette syndrome, epilepsy, depression, bipolar disorder and schizophrenia. Pertwee is particularly optimistic that cannabis will help people with post-traumatic stress disorder. Experiments in rats show that THC "speeds up the rate at which the animals forget unpleasant experiences," he says. And a recent study in people with PTSD showed that THC capsules improved sleep and stopped nightmares.

Despite these heady beginnings, medical cannabis still faces an uphill climb. Although some states have sanctioned its use, no smoked substance has ever been formally approved as a medicine by U.S. regulatory agencies. Smoking cannabis can lead to chronic coughing and bronchitis, and smoking renders a drug off-limits for children, Mechoulam notes.

THC pills don't have these downsides, but the drugs have received only lukewarm acceptance. Despite smoking's drawbacks, "it is seen as better because you can regulate the amount of THC you're getting by not puffing as much," says pharmacologist Daniele Piomelli of the University of California, Irvine. Cap-

C. BLÁZQUEZ

sules can cause dizziness and make it hard to focus. "Patients suffering from neuropathic pain or depression don't want to be stoned — they want relief," he says.

Controlled, randomized trials that seek to clarify whether smoked cannabis delivers on its medical promise — with acceptable side effects — have been hard to come by. But scientists in California have recently concluded several studies in which patients with severe pain received actual cannabis cigarettes or cannabis cigarettes with the cannabinoids removed.

In one trial, researchers randomly assigned 27 HIV patients to get the real thing and 28 to get fake joints. All the patients had neuropathic pain, in which neurons can overreact to even mild stimuli. About half of the people getting real cannabis experienced a pain reduction of 30 percent or greater, a standard benchmark in pain measurement. Only one-quarter of volunteers getting the placebo reported such a reduction.

"That's about as good [a reduction] as other drugs provide," says Igor Grant, a neuropsychiatrist at the University of California, San Diego, who is among the scientists overseeing the trials.

While such studies provide evidence that smoked marijuana has medical benefits, future trials are more likely to explore the benefits of cannabis derivatives that don't carry the baggage that smoking does.

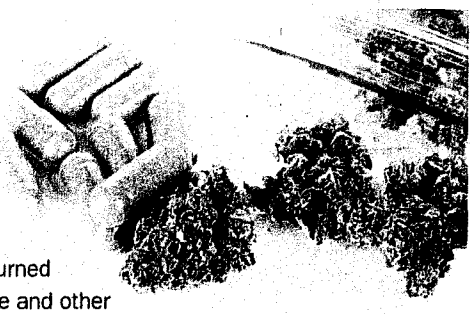
Ultimately, the fate of medical cannabis and its derivatives will rest on the same make-or-break requirements that every experimental medicine faces — whether it cures a disease or alleviates its symptoms, and whether it's tolerable.

"We have to be careful that marijuana isn't seen as a panacea that will help everybody," Grant says. "It probably has a niche.... We can't ignore the fact that cannabis is a substance of abuse in some people." ■

Explore more

- A. Hazekamp and F. Grotenhermen. "Review on clinical studies with cannabis and cannabinoids 2005–2009." *Cannabinoids*. 2010.

Getting cannabis in



When most people think of medicinal cannabis, smoking comes to mind. Though smoking works quickly and allows users to regulate their intake, it's hardly a scientific approach: Cannabis quality is often unknown, and inhaling burned materials is bad for the lungs. These and other drawbacks have spawned new ways to consume medical marijuana.

Some people inhale cannabis by using a device that heats the plant without igniting it. This vaporization unleashes many of the same cannabinoid compounds as smoking does, without the combustion by-products, researchers say. Anecdotally, patients report that the effect is prompt, on a par with smoking.

Because cannabis derivatives can pass through the lining of the mouth and throat, a company called GW Pharmaceuticals has devised a spray product called Sativex. This drug contains roughly equal amounts of two key cannabinoids — THC and CBD — plus other cannabis components in an alcohol solution. A dose of Sativex is sprayed under the tongue; no smoking required.

In the face of these options, the "pot pill" seems almost passé. But capsules of synthetic THC exist. One called Marinol has been approved in the United States since 1985, and another called Cesamet was cleared more recently. Doctors can prescribe the drugs for nausea, vomiting, loss of appetite and weight loss. Though sales of capsules have increased recently, many users complain of psychoactive side effects and slow action. — *Nathan Seppa*

Medical marijuana's various forms

Name of drug	Ingredients/ delivery	Where approved	Uses	Drawbacks (partial list)
Marinol (dronabinol)	THC/capsule	United States, Canada	Nausea, weight loss, appetite stimulant	Needs to be swallowed, slow to act, psychoactive effects
Cesamet (nabilone)	THC/capsule	United States, Canada, United Kingdom	Nausea, weight loss, appetite stimulant	Needs to be swallowed, slow to act, psychoactive effects
Sativex	THC, CBD and other cannabinoids/spray	Canada	Cancer pain, multiple sclerosis	Contains alcohol that can irritate the mouth
Cannador	THC and CBD/ capsule	Not approved	Tested against multiple sclerosis and other diseases	Needs to be swallowed, slow to act
Cannabis, hashish, marijuana	THC and 60-plus other cannabinoids/ typically smoked or heated into a vapor and then inhaled	Not approved as a drug but sanctioned for medical use in 14 U.S. states, Canada, the Netherlands, Israel	Nausea, appetite stimulant, pain, anxiety, depression and other ailments	Lung irritation from smoke, variable dosing, psychoactive effects, increased heart rate, decreased blood pressure

CHARLOTTELAKE/ISTOCKPHOTO